REMARKS

Claims 1-45 were pending for consideration. In this Amendment, applicants have canceled claims 1-8, 10-13 and 17-29 and added new claim 46. Support for the claim amendments is found throughout the specification. For the recitation of "aryl" in claim 30, additional support may be found, for example, on page 16, first paragraph, of the specification. No new matter has been added. Applicants note that new claim 46 corresponds to prior claim 13 with the modification that all the formulas except I13 or I13a have been cancelled. Applicants note that all of the claims now depend, directly or indirectly, from claim 30.

The foregoing cancellation of claims should in no way be construed as acquiescence to any of the Examiner's rejections and were made solely to expedite prosecution of the application, and in order to narrow the outstanding issues for appeal, if an appeal becomes necessary. Applicants reserve the right to pursue claims to the canceled subject matter, or any subject matter which they are entitled to claim, in this or a separate application.

REJOINDER

It is respectfully requested that upon allowance of the claims under examination, that the withdrawn method claims be rejoined, as set forth under the MPEP.

REJECTIONS

Enablement Rejections

The Examiner has rejected claims 1-13, 17 and 29-34 as allegedly non-enabled. Applicants respectfully traverse this rejection.

In response to the Examiner's rejection, applicants have deleted "derivatives" and "solvates" from the claims and have defined "aryl" in claim 30.

With respect to claim 30, applicants submit that, in view of the specification, the skilled artisan, at the date of filing, would have been enabled to synthesize and use as mitotic protein inhibitors the claimed compounds of formula IA4 without undue experimentation.

The compounds of claim 30 are hexahydropyranoquinoline derivatives (see Example 1 and Example B in the specification). With regard to the synthesis of the compounds of claim 30, it would have been, at the time of filing, a matter of routine skill in the art for to provide appropriate starting materials by adding the CH_2R^a group to 3,4-dihydro-2H-pyran. Such substituted 3,4-dihydro-2H-pyrans are commercially available, known in the literature and/or prepared by methods that are known in the art and are described in the literature, see for example, the standard chemical treatise of Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag (Stuttgart) and are further shown, for example, on page 38 of the specification.

Furthermore, applicants submit herewith Rule 132 declarations of, respectively, co-inventors Kai Schiemann and Frank Zenke and of Jan Hauss, an employee of Merck KGaA, an affiliated company of the assignee Merck Patent GmbH. These declarations provide data related to the synthesis, characterization and activity for a multitude of compounds falling within claim 30. The synthesis protocols and methods for obtaining the activity data reported in the declarations are set forth in the declarations and are according to conventional methods in the art, which were known to the skilled artisan at the date of filing. The declarations demonstrate significant activity of compounds falling within claim 30 with regard to inhibiting mitotic motor protein Eg5.

As discussed, for example, on pages 1-3 of the specification, mitotic motor protein Eg5 is invovled in the regulation of the formation and dynamics of the cellular spindle apparatus, which is responsible for correct and coordinated alignment and

separation of the chromosomes and the upregulation of the motor protein Eg5 has been found, for example, in tissue from breast lung and colon tumours. The inhibition of Eg5, as demonstrated in the declarations, is therefore reasonably correlative of a utitilty which is fully supportive of the enablement of claim 30.

Accordingly, applicants submit that the skilled artisan, at the date of filing, would have been enabled to make (e.g., to synthesize) and to use (e.g. to inhibit mitotic motor protein Eg5) compounds commensurate with the scope of claim 30, without undue experimentation. Accordingly, applicants respectfully request reconsideration and withdrawal of the enablement rejection of claim 30 and of the remaining claims, each of which depend, directly of indirectly, from claim 30.

Novelty Rejections

The Examiner has rejected claims 1-13, 17 and 29-34 as allegedly anticipated by (1) WO 9408051 in view of its English language U.S. counterpart Patent No. 6,001,579 and (2) Baudelle et al. (1998) Tetrahedron 54: 4125. Applicants respectfully traverse this rejection and submit that neither of these references discloses a 3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline scaffold, which is substituted at the tetrahydropyranyl ring by CH_2R^a as is set forth in claim 30. Because claim 30 is novel over the cited art, applicants submit that the remaining claims, which depend from claim 30, are also novel over the cited references. Accordingly, reconsideration and withdrawal of the anticipation rejection is respectfully submitted.

Obviousness Rejections

The examiner has rejected claims 1-13, 17 and 29-34 as allegedly obvious over Baudelle et al. (1998) Tetrahedron 54: 4125. Applicants respectfully traverse this rejection.

Claim 30 differs from Baudelle at least in that claim 30 defines compounds that are specifically substituted at the tetrahydropyranyl ring by CH_2R^a. This defined

chemical substitution has the effect of specifically inhibiting mitotic motor proteins, and in particular Eg5, as discussed above. As discussed in the specification, for example, on page 2, the specific inhibition of Eg5 is advantageous in that it avoids the concomitant neuropathological side effects found, for example, with Taxol.

There is no teaching in the prior art that would have motivated the skilled artisan to modify the compounds of Baudelle in order to arrive at the compounds of claim 30. In contrast, the unpredictability of the prior art renders such modifications non-obvious. In this regard, applicants direct the Examiner to page 10 of the Office Action which states that the results of substituting a methyl for a hydrogen in a drug molecule may not be predicted in advance: "even a difference of a methyl group versus hydrogen changes [drug] properties altogether." Applicants further direct the Examiner to page 10 of the Office Action which states that the "pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity."

Accordingly, due to the unpredictable nature of the prior art, applicants submit that the skilled artisan would not have been motivated, with a reasonable expectation of success, to modify 3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinolines as set forth in claim 30.

Moroever, Baudelle et al. (1998) Tetrahedron 54: 4125 does not relate to Eg5 modulators or to compounds for the treatment of cancer or other hyperproliferative diseases. Accordingly, the skilled artisan would not have been directed by the reference to even assess modifications directed to mitotic motor protein inhibition.

For at least the foregoing reasons, applicants submit that claim 30 is non-obvious over the Examiner's rejection. Applicants submit that the remaining claims, which depend from claim 30, are therefore necessarily also non-obvious over the cited reference. Accordingly, reconsideration and withdrawal of the obviousness rejection is respectfully submitted.

Provisional Double Patenting Rejections

As permitted under the MPEP, applicants respectfully request that the provisional double patenting rejections be held in abeyance until the cited claims have been patented.

CONCLUSION

In light of the above amendments and comments, Applicants respectfully request that all rejections and objections be withdrawn and that a timely Notice of Allowance should be issued in this application.

Should the Examiner believe that anything further is necessary in order to place this application in better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below.

In the event that additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefore are hereby authorized to be charged to our Deposit Account No. 01-2300 referencing docket number 030863-00040.

Respectfully submitted,

Ronald J. Kamis
Registration No. 41,104

Customer No. 004372
ARENT FOX LLP
1050 Connecticut Avenue, N.W.
Suite 400
Washington, D.C. 20036-5339
Telephone: (202) 857-6000
Facsimile: (202) 857-6395